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TITLE: Investigate the Role of Obesity in Ovarian Cancer Initiation and Progression

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

During this funding period we focused on generating the mouse models that will enable achieve the goals of the proposed research. The aim of this project is to identify genes and pathways in ovarian stem cells and in transformed ovarian cells affected by obesity that lead to ovarian cancer initiation and progression.

15. SUBJECT TERMS

Obesity, Ovarian Cancer, ovarian stem cells, inflammation, adipose tissue

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1. Introduction

The objective of this project is to determine the effects of obesity on ovarian stem cell activity (ovarian stem cells are prone to tumorigenesis) as well as the growth and metastatic potential of transformed ovarian epithelial cells in obese animals. The goal is to identify genes and pathways that lead to ovarian cancer initiation and progression. We also aim to identify secreted factors from adipose tissue that promote ovarian cancer initiation and progression in obesity. Identification of new genes and pathways will set the basis for the development of new therapeutics. Given that SIRT1 activity in adipose tissue protects from obesity-related metabolic dysfunction and inflammation, we will also test the hypothesis that adipose SIRT1 counteracts ovarian cancer initiation and progression and its loss in obese animals contributes to ovarian cancer. As SIRT1 can be pharmacologically activated, combinatorial therapies that target ovarian cancer cells and induce SIRT1 activity in adipose tissue might prove a powerful approach in treating patients.

2. Keywords

Obesity
Adipose tissue
Inflammation
SIRT1
Ovarian stem cells
Ovarian cancer

3. Accomplishments

-What were the major goals of the project?

Major Goals for year 1 (from statement of work)

1. Determine the effects of high-fat diet and adipose SIRT1 on the ovarian stem cell niche.
   Major Task 1: Determine the effects of high-fat diet on the ovarian stem cell niche
   Subtask 1: Generate mice with EGFP expressing-ovarian stem cells, which will be fed high-fat and chow diets.
   Subtask 2: High-fat and chow diet feeding for 1-5 months.
   Subtask 3: Analyze ovaries (histology) and ovarian stem cell activity (in vitro).
   Milestones:
   Local IRB/IACUC Approval (for all procedures/subtasks)
   ACURO Approval (for all procedures/sutasks)
   Analysis of ovarian stem cell activity in obesity
   Major Task 2: Identification of genes and pathways in ovarian stem cells affected by high-fat diet
   Subtask 1: Gene expression analyses of the ovarian stem cells isolated from mice fed high-fat and chow diets for 4, 8, 16, and 20 weeks.
   Subtask 2:
   Gene expression analyses of adipose tissue and cytokine/adipokine arrays using serum and peritoneal fluid of the mice used in major task 2/ subtask 1.

Subtask 3: Test the effects of the identified secreted factors on primary ovarian stem cells.
Milestones:
Identification of targets in ovarian stem cells influenced by obesity.
Identification of secreted factors from adipose tissue that affect ovarian stem cells.
Major Task 3: Determine the effects of adipose SIRT1 on ovarian stem cells
Subtask 1: Generate SIRT1 adipose tissue-specific knockout (FKO) and transgenic (FTg) mice with EGFP-expressing ovarian stem cells.

2. Determine the effects of high-fat diet and adipose SIRT1 on ovarian cancer.
Major Task 4: Determine the effects of high-fat diet on ovarian cancer initiation.
Subtask 1: Generate mice with ovarian stem cells null for p53 and Rb.

What was accomplished under these goals?

During the first year of funding we obtained approval from the local IRB/IACUC and the ACURO, both of which were lengthy processes of multiple revisions. Our protocol had also to be reviewed again by the ACURO as the local protocol expired after few months of the first ACURO approval.

Our studies require the generation of cohorts of female mice with certain genotypes. This process took longer than anticipated due to breeding problems. We have now enough female mice of similar ages expressing EGFP in ovarian stem cells that we will feed high fat diet and we will proceed with the analyses. Most of the analyses listed as milestones required the mice, which took us longer than anticipated to generate.

We have also generated mice that are homozygotes for the conditional p53 and Rb alleles, and express the cre recombinase under the LGR5 promoter in order to drive the excision specifically in stem cells. This breeding scheme was particularly demanding, but we have now enough mice to proceed with the experiments.

What opportunities for training and professional development has the project provided?
Nothing to report

How were the results disseminated to communities of interest?
Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?
We plan to proceed with the experiments of high fat diet feeding and the analysis of ovarian stem cells. We also plan to induce tumorigenesis to the mouse models of ovarian cancer and proceed with the experiments described in the proposal. We also plan to generate mice that are also SIRT1 KO or transgenic specifically in adipose tissue and proceed with the experiments described.

4. Impact

What was the impact on the development of the principal disciplines of the project?
Nothing to report

What was the impact on other disciplines?
Nothing to report

What was the impact on technology transfer?
Nothing to report

What was the impact on society beyond science and technology?
Nothing to report

5. Changes/Problems

Changes in approach and reasons for change
Nothing to report

Actual or anticipated problems or delays and actions or plans taken to resolve them
The generation of mice took longer than anticipated because not enough mice were produced. Now we have enough mice to proceed with experiments.

Changes that had a significant impact on expenditures
Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report

Significant changes in use or care or human subjects
Nothing to report

Significant changes in use or care or vertebrate animals
Nothing to report

Significant changes in use of biohazards and/or select agents
Nothing to report

6. Products
Nothing to report

7. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name: Leonard P. Guarente
Project Role: PI
Nearest person month worked: 0.5 month (summer)
Contribution to the project: Project guidance

Name: Angeliki Chalkiadaki
Project Role: Research scientist
Nearest person month worked: 12 months
Contribution to the project: All the experiments described in the proposal.

Has there been a change in the active other support of the PD/PI or senior/key personnel since the last reporting period?
Nothing to report

What other organizations were involved as partners?
Nothing to report

8. Special Reporting Requirements
Not applicable

9. Appendices
Not applicable